Sex and Gender Influences on the Cardiovascular Health of Women

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Mid-Life and Older Women’s Health
September 13, 2018
Advancing the Health of Women in Mid-Life and Beyond

- Life-Expectancy and Leading Causes of Morbidity and Mortality
- Sex Differences in Burden of Cardiovascular Disease
- Hypertension as a Key Driver of Cardiovascular Disease in Women
- The Heart-Brain Connection: Shared Risk Factors and Implications
  - Cognitive Impairment and Dementia
- Addressing the Health Challenges of Mid-Life and Older Women a Research Agenda
  - Leveraging a Longstanding Legacy
  - Seizing Opportunities for the Future
On Average, Women Live Longer Than Men

Life expectancy has increased over decades, though differences exist by race and sex.

Thus, women represent a large proportion of the older US population and experience health issues of older age including:

- Heart disease as the leading cause of death
- Cardiovascular diseases and specifically those of high prevalence in women
  - Hypertension
  - Heart Failure
  - Stroke
- Cognitive Impairment and Dementia

NCHS, Health, United States, 2016, Figure 6. Data from the National Vital Statistics System (NVSS).
Heart Disease is the Leading Cause of Death in the United States and Prevalence Increases with Age.

1 of every 4 female deaths is due to heart disease.

CVD prevalence increases with age. More American women die each year from CVD than all cancers combined.

NCHS, Health, United States, 2016, Figure 8. Data from the National Vital Statistics System (NVSS).
Key Differences Between Men and Women in Cardiovascular Disease

▪ **Prevalence and Mortality** Absolute numbers of individuals living with and dying from CVD in US higher for women than men.

▪ **Known Differences** Epidemiology and clinical presentation may differ between men and women.

▪ **Known Disparities** Clinical outcomes among women have not improved at the same rate as men. Disparities exist in the application of evidence-based therapies.

▪ **Scientific Importance of Sex as a Biological Variable** Sex-specific pathophysiology influences outcomes.

Differences in Burden of CVD Between Sexes
Beyond the Peak: Narrowing the Sex Gap

Cardiovascular Disease Statistics

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (2015, all ages)</td>
<td>422,355 (51%)</td>
<td>414,191 (50%)</td>
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<tr>
<td>Prevalence (2011-14, age ≥20y), millions</td>
<td>44.3 (37%)</td>
<td>47.8 (36%)</td>
</tr>
<tr>
<td>Hospital discharges (2010)</td>
<td>2,571,000</td>
<td>2,220,000</td>
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CVD Mortality Trends
Since the mid-80’s CVD mortality in women exceeded that of men, until 2013 when the sex gap narrowed.
Addressing the Unique Challenges of Acute Myocardial Infarction in Women

State of the Science of AMI in Women

Women present with AMI at an older age with more comorbidities and have more complications of AMI as compared to men.
**Stroke mortality, prevalence, and hospitalizations in women exceed men.**

- Each year ~55,000 more females than males have a stroke.
- Females have a higher lifetime risk of stroke than males.
  - 1 in 5 for females compared to 1 in 6 for males 55 to 75 years of age
- In the oldest age groups, age-specific incidence in females ≥ males

<table>
<thead>
<tr>
<th>CVD Statistics - Stroke</th>
<th>Men</th>
<th>Women</th>
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</thead>
<tbody>
<tr>
<td>Mortality (2015, all ages)</td>
<td>58,288 (42%)</td>
<td>82,035 (58%)</td>
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<tr>
<td>Prevalence (2014, age ≥20y), millions</td>
<td>3.1 (2%)</td>
<td>4.1 (3%)</td>
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<tr>
<td>Hospital discharges (2014)</td>
<td>434,000</td>
<td>454,000</td>
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</table>
Heart failure mortality and hospitalizations in women exceed men.

- HF disproportionately affects older adults
  - 80% of cases occur in individuals ≥ 65 years.
- U.S. population ≥65 years will double by 2050, with women outnumbering men.
- 40-70% incident HF occurs as HFpEF, which is more common in women.

### CVD Statistics – Heart Failure

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<tr>
<td>Mortality (2015, all ages)</td>
<td>33,667 (45%)</td>
<td>41,584 (55%)</td>
</tr>
<tr>
<td>Prevalence (2011-14, age ≥20y), millions</td>
<td>2.9 (2%)</td>
<td>3.6 (3%)</td>
</tr>
<tr>
<td>Hospital discharges (2014, all ages)</td>
<td>462,000</td>
<td>438,000</td>
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</table>

HTN occurs in more women than men. After 60 years, prevalence becomes higher in women than men, and gap widens with aging related to the large proportion of older women.
Heart Failure as a Complication of Hypertension: Increasing Prevalence with Age

<table>
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<th>Population-attributable risk by race and ethnicity for HF</th>
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<tr>
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<tr>
<td>In Utero</td>
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<tr>
<td>Childhood</td>
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<tr>
<td>Adolescence</td>
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<tr>
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<td>Middle Adulthood</td>
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<tr>
<td>Late Adulthood</td>
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</table>

**HFpEF**
- Population Attributable Risk (%)
  - Overall: 40.9
  - Caucasian: 12.3
  - African American: 40.7
  - Hispanic: 53.6
- Population Attributable Risk (%)
  - Overall: 10.1
  - Caucasian: 9.6
  - African American: 12.3
  - Hispanic: 8.2

**HFrEF**
- Population Attributable Risk (%)
  - Overall: 42.7
  - Caucasian: 13.5
  - African American: 19.0
  - Hispanic: 41.1
- Population Attributable Risk (%)
  - Overall: 12.6
  - Caucasian: 10.8
  - African American: 6.6
  - Hispanic: 4.5

Physical Activity in Women Associated with Reduced Risk of Heart Failure

Higher levels of physical activity and walking were associated with reduced risks of developing HF in later life. With continued growth in number of older women and challenges in treating HFP EF, physical activity may hold hope for HF prevention.

LaMonte M et al. JACC: Heart Failure Sep 2018, 936; DOI: 10.1016/j.jchf.2018.06.020
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The Heart-Brain Connection: Critical Intersection of Sex and Shared Risk Factors

**Diabetes**: Powerful risk factor, disproportionate increased risk of CHD for women vs. men.

**Obesity**: 41% of US women are obese; 10% extremely obese. Heaviest category with 4x risk for CV events.

**Hypertension**: Antecedent to MI, Stroke, Heart Failure, Dementia. Prevalence increases with age.

**Smoking**: 25% increased CHD risk among female as compared to male smokers.

CVD and Broader Health Implications
As Women Age
Challenges with Cognition and Independent Living Increase

**CDC/NCHS, Health, United States, 2015, Figure 6. Data from the National Health Interview Survey (NHIS).**
The Heart-Brain Connection: Addressing Shared Risk of Hypertension as Key Driver of CVD, Cognitive Decline, and Dementia

A Randomized Trial of Intensive vs. Standard BP Control

Intensive management of SBP to target <120 mmHg reduced complications of high BP by 25% and death by 27% as compared to SBP target <140 mm Hg.

SPRINT-MIND Memory and Cognition in Decreased Hypertension

Intensive management as compared to standard also reduced:
- Rate of incident mild cognitive impairment (MCI)
- MCI + dementia combined
- Smaller increases in white matter lesions on MRI
Vascular dementia and Alzheimer’s disease share underlying disease mechanisms.

ApoE gene increases risk of both Alzheimer’s disease and atherosclerosis.

The effect of ApoE on risk of dementia is stronger in women.

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Women’s Health Research at NHLBI: Longstanding Legacy and New Directions

**Initiatives/Programs**

- **Physical Activity and CVD**
  - Objective Physical Activity and CV Health (OPACH)
    - Both light-intensity & moderate-vigorous PA associated with lower mortality
  - WHI Strong and Healthy (WHISH)
    - Trial of ~50K older women testing whether ↑PA will reduce CV events
  - WHISH-2 Prevent Heart Failure Study
    - RCT to evaluate effect of PA and strength training on HF in elderly women
- **CVD, sleep, and cognitive decline**
  - WHI Memory Study
    - CVD, high BP, and diabetes associated with cognitive decline in older women
  - WHI Sleep Hypoxia Effects on Resilience (WHISPER)
    - Impact of sleep-disordered breathing on CV events & cognition in older women
- **Future Directions**
  - Precision Medicine
  - Healthy Aging and CV Health; Resilience
  - CVD Among Older Women (avg. age 83 years)

Aligning Institute-Solicited Science with the Strategic Vision Goals & Objectives

- **Objective 1:** Normal Biology
- **Objective 2:** Pathobiology, Onset, & Progression of HLBS Diseases
- **Objective 3:** Population Differences
- **Objective 4:** Precision Medicine
- **Objective 5:** Novel Diagnostics & Therapeutics
- **Objective 6:** Clinical & Implementation Research
- **Objective 7:** Data Science
- **Objective 8:** Workforce & Resources

**Life Stages:**
- In Utero
- Childhood
- Adolescence
- Early Adulthood
- Middle Adulthood
- Late Adulthood
Aligning Institute-Solicited Science with the Strategic Vision Goals & Objectives

Objective 1: Normal Biology
- Resilience (e.g. estrogen effects)
- Transgenerational studies

Objective 2: Pathobiology, Onset, & Progression of HLBS Diseases
- Disease mechanisms and presentation (i.e. MI in younger women)

Objective 3: Population Differences
- Sex differences studies; sex-specific studies related to conditions that are more prevalent or differentially affect women (e.g., microvascular disease, COPD)

Objective 4: Precision Medicine
- Risk prediction and treatment (e.g., HFpEF)
- Precision medicine and trans-omics research

Objective 5: Novel Diagnostics & Therapeutics
- Biomarkers of disease (Men vs Women)

Objective 6: Clinical & Implementation Research
- Clinical trial science, sex-specific analyses, inclusion gaps
- Registries for rare diseases (e.g., SCAD); IS to eliminate care/management disparities

Objective 7: Data Science
- Genome-phenome activities
- Meta-analyses of Clinical Trial endpoints in women

Objective 8: Workforce & Resources
- Multidisciplinary/team science

Women’s Health Priorities Span Every Objective of the NHLBI Strategic Vision
Sex as the Highest Order of Precision Medicine

How do clinical factors interact with exposures, differential risk factors, and their potency, genetic susceptibility, and lifestyle and social determinants of health in pathways of heart, lung, blood, and sleep dysfunction?
Advancing Precision Medicine Science: Early vs. Late Postmenopausal Hormone Therapy

Vascular Effects of Early versus Late Postmenopausal Treatment with Estradiol

Howard N. Hodis, M.D., Wendy J. Mack, Ph.D., Victor W. Henderson, M.D., Donna Shoupe, M.D., Matthew J. Budoff, M.D., Juliana Hwang-Levine, Pharm.D., Yanjie Li, M.D., Mei Feng, M.D., Laurie Dustin, M.S., Naoko Kono, M.P.H., Frank Z. Stanczyk, Ph.D., Robert H. Selzer, M.S., and Stanley P. Azen, Ph.D., for the ELITE Research Group

Effects of estradiol on progression of atherosclerosis, assessed as CIMT, differed according to the time of initiation of therapy, with benefit when initiated at <6 years past menopause but not when initiated ≥6 years past menopause.
TOPMed: A Diverse Genome-Phenome Resource Enabling Data Science for an Innovative Women’s Health 2.0 Agenda

Phenotype Diversity

- Heart, 38%
- Lung, 34%
- Blood, 8%
- Multi-phenotype, 20%

Objective 4: Precision Medicine

58% women in WGS samples publicly available for research

An expansive data resource, with rich phenotype and population diversity, for scientific exploration, including **sex-specific and sex-difference** analyses.

PHENOTYPE DIVERSITY represents 144K WGS samples from Phase 1-4 X01s.
Addressing the Cardiovascular Health of Women

**What if** We Could Leverage Deep Characterization, Genomics, and Data Science for Transformative Impacts on the Health of Women?

- The promise of precision medicine, when fully realized embraces...
  - Sex as the highest order of risk assessment, prevention, diagnosis, and treatment
  - Diagnostics that reflect contribution of sex-based biomarkers
  - Tailored therapeutics that address hormone and age-related influences on health and disease
  - Clinical research that advances sex-specific analyses to eliminate gaps in evidence-based care of women

Protective effects of estrogen in early life and post-menopausal transitions that confer vascular risk

Targets of intervention early in life to portend improved long-term CVD and cognitive outcomes for women

TOPMed

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